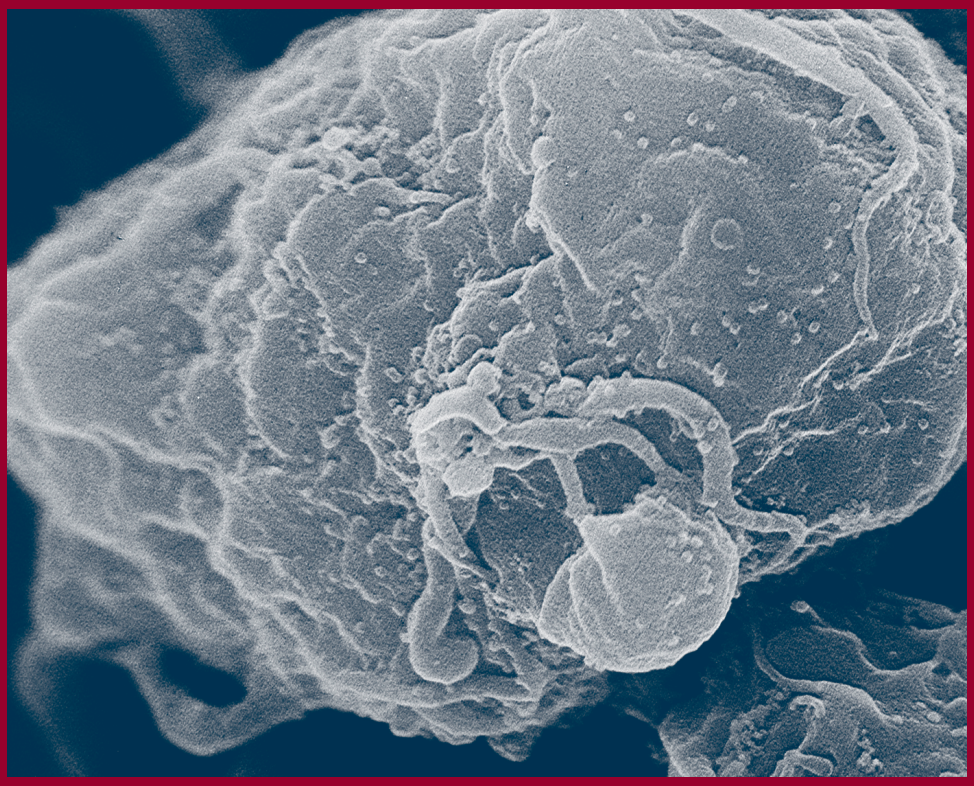

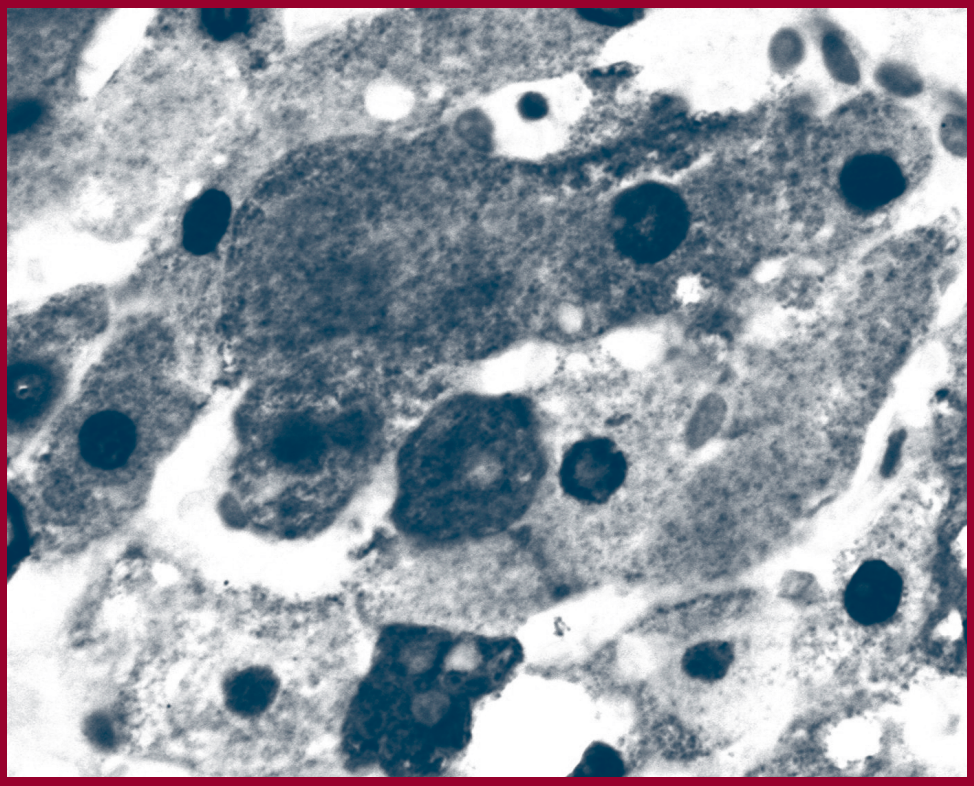

Liver disease is a common health concern and leading cause of death in people infected with the human immunodeficiency virus (HIV).

TOP: A scanning electron micrograph shows HIV viruses, visible as small round bumps, budding from the surface of a lymphocyte (immune cell) in culture. Photo: Public Health Image Library, Centers for Disease Control and Prevention/ Drs. C. Goldsmith, P. Feorino, and E. L. Palmer.

BOTTOM: Liver cells from an HIV-infected individual stained using an antibody against the hepatitis B core antigen protein (color of stain altered for publication) indicate large amounts of hepatitis B virus (HBV, dark blue) in most cells. Coinfection with HBV is common in HIV-positive patients. Photo: Dr. Zachary Goodman, Division of Hepatic Pathology, Armed Forces Institute of Pathology.

CHAPTER 6:
HIV AND LIVER DISEASE

INTRODUCTION AND BACKGROUND

Liver disease is an important cause of morbidity and mortality in persons infected with human immunodeficiency virus-1 (HIV). The types of liver disease that occur in HIV-infected persons include those that also affect persons without HIV (e.g., hepatitis B and C, nonalcoholic steatohepatitis, alcoholic liver disease, and drug-induced liver disease), as well as opportunistic infections of the liver and biliary tree (e.g., atypical mycobacterium, cryptosporidiosis, cytomegalovirus, and immunodeficiency-associated cancers such as lymphoma). However, the incidence and severity of liver disease in HIV-infected persons often differ from other patient populations and have changed markedly since the advent of highly active antiretroviral therapy (ART) in 1996.

Before the availability of ART, opportunistic infections, such as those caused by *Mycobacterium avium* complex or HIV-related cholangitis, dominated the expression of liver disease and patient survival. Now, in HIV-infected persons taking ART, liver disease caused by chronic viral hepatitis has emerged as a leading cause of death, due in large part to HCV coinfection resulting from a shared transmission route for the two viruses. HCV infection is adversely affected by coinfection with HIV at every stage of its natural history—the proportion of patients who recover is much lower. In the United States, approximately 25 percent of HIV-infected persons are coinfected with hepatitis C virus (HCV) and 8 percent have chronic hepatitis B. Whereas liver disease accounted for less than 3 percent of deaths among HIV-infected persons before ART was available, in more recent years, 10 to 13 percent of mortality is classified as liver-related. Indeed, in some clinics, the majority of deaths in HIV-infected persons are due to liver disease.

The frequency of liver disease in HIV-infected persons also varies by ethnic/racial group and risk category. HCV coinfection is most frequent among HIV-infected persons who are African American and those who acquired HIV from illicit drug use or contaminated clotting factor treatments for hemophilia. In contrast, hepatitis B virus (HBV) coinfection is most common among HIV-infected gay men. HBV coinfection is also likely to be a very important problem in HIV-infected persons in Asia and Africa. Strategies to reduce the risk of viral hepatitis are also limited in HIV-infected persons who have diminished responses to vaccines and available treatments.

Further complicating the management of liver disease in HIV-infected persons is evidence that HIV therapy with ART also causes liver disease. Liver enzyme levels increase markedly in 5-10 percent of persons starting ART, particularly in those coinfected with HCV or with chronic hepatitis B. Antiretroviral use is also associated with steatohepatitis and mitochondrial injury.

Clearly, as therapies for HIV have improved and survival has been extended by antiretroviral therapy, liver disease has become a critical problem among HIV-infected persons.

RECENT RESEARCH ADVANCES

Important advances have been made in research on liver disease in HIV-infected patients.

Epidemiology and Management: Past research on liver disease in HIV-infected persons has focused on epidemiology and health outcomes, particularly in those coinfected with HCV. Research advances include:

- Demonstration of the high prevalence of HCV and HBV infections among HIV-infected persons;
- Characterization of the natural history of liver disease in those coinfected with HIV and either HCV or HBV;
- Evaluation of the response of HIV-infected persons to available vaccinations and treatments for viral hepatitis;
- Delineation of the risk of antiretroviral-related hepatitis, including interaction with chronic HBV and HCV infections;
- Recognition of the link between antiretroviral use and fatty liver disease, mitochondrial injury, and lactic acidosis;
- Assessment of the effects of HCV and HBV coinfection on the course and treatment of HIV;
- Description of the efficacy of antiviral therapy for hepatitis C in HIV-infected persons in randomized trials; and
- Description of successful liver transplantation for HIV-infected persons with end-stage liver disease due to hepatitis B and C.

In addition, there are promising clinical studies under way to study the effects of antiretroviral therapy on the liver and on the immune response to HCV infection. There is also ongoing research to evaluate virologic and immunologic interactions between HIV and HCV infection.

Pathogenesis: Despite these numerous advances, efforts to understand the pathogenesis of liver disease in HIV-infected persons have been substantially constrained by the absence of relevant experimental models, and by the difficulty of disentangling potentially confounding conditions in humans, such as the interactions among alcohol, viral hepatitis, antiretroviral drug use, and injection drug use. In particular, there are no cell lines or animal models that serve as tractable systems to propagate HIV together with either HBV or HCV. Likewise, studies of the effects of antiretroviral drugs on the liver are limited by species differences in the metabolism and toxicities of these drugs in humans and experimental animal models.

Research Challenges: There are also major limitations to clinical research, including difficulties accurately measuring the use of alcohol, illicit drugs, and antiretroviral compounds, thereby reducing the ability of the researcher to control for these factors in clinical studies. Finally, information on the treatment of HCV and HBV infections in HIV-infected persons has been limited and delayed. Increased multidisciplinary basic, clinical, and translational research in these areas is of critical importance to reducing the burden of liver disease in HIV-infected persons.

RESEARCH GOALS

The major goals for research in HIV and liver disease are to define the causes of liver disease associated with HIV and to develop means to prevent and treat liver disease in HIV-infected persons.

Basic and Laboratory Research: Research on liver disease in HIV-infected persons is limited largely to patient-based research because of the lack of *in vitro* and *in vivo* models of coexistent HIV infection

and liver disease. Small animal models or cell culture systems that reflect the complexity of this problem would be extremely helpful to studies of the pathogenesis of HIV-associated liver disease, but their development is probably a high-risk, long-term goal.

- *Research Goal:* To develop *in vitro* and *in vivo* models of HIV and liver disease (Matrix Cell C3).

Most information suggests that the deleterious effect of HIV on the liver is indirect, likely mediated by changes in immune function or cytokine release rather than direct effects of HIV on liver cells. Both HIV-HBV and HIV-HCV interactions are important areas of research focus. Furthermore, immune dysregulation and cytokine release caused by HIV infection may have profound effects on how hepatocytes respond to injury and may affect function of other parenchymal cells such as endothelial, stellate, and Kupffer cells.

- *Research Goal:* To define the effects of HIV infection on different liver cell types (Matrix Cell A3).

These basic investigations into the effects of HIV infection on the liver and how it responds to injury are likely to provide insights into the problems of liver disease in HIV-infected patients.

Epidemiology: Better information on the prevalence, severity, etiology, and natural history of liver diseases in HIV-positive persons would advance knowledge in this area. There is great variability in the prevalence of liver disease in different ethnic, racial, geographic, and risk-group cohorts of patients with HIV infection. Liver disease is not always adequately evaluated in these cohorts. With the rising mortality rates from liver disease in HIV-infected persons, it is important that liver disease be actively diagnosed and approaches to prevention and treatment adopted in this patient population. These epidemiological studies could include careful analyses of alcohol intake, nutrition, hepatitis markers, medication history, and risk factors for nonalcoholic fatty liver disease (e.g., body mass index and body fat distribution; diabetes; glucose, insulin, and adiponectin levels; and waist-hip ratios).

- *Research Goal:* To define the prevalence, severity, and etiology of liver diseases in different subgroups of HIV-infected persons (Matrix Cell B1).

Ideally, the status of liver disease in these cohorts would also be studied prospectively. A particularly important cohort of patients with HIV are those in developing nations where HIV is common and ART therapy is now being introduced through global programs. These individuals may be at greater risk of liver disease due to hepatitis B, which is an almost universal infection of childhood in much of Asia and Africa. Rates for carriers of hepatitis B surface antigen (HBsAg), a sign of current HBV infection, in these countries range from 5 to 15 percent in young adults, and those without HBsAg usually have antibody to HBV, either to the core antigen, anti-HBc, and/or to the surface antigen, anti-HBs, indicating a past HBV infection. Progression of AIDS and reconstitution of the immune system with ART may cause worsening of liver disease in HBsAg carriers and reactivation of hepatitis B with return of HBsAg in those with antibody to HBV alone.

- *Research Goal:* To define factors that are responsible for HBV reactivation in HIV-infected persons and to evaluate means of its prevention (Matrix Cell B2).

Clinical Investigation of Prevention and Diagnosis: The interactions of HIV with either HCV or HBV are by necessity investigated in human subjects. These investigations can be part of cross-sectional surveys or natural history studies of HIV, but are best done as a part of therapeutic trials of treatment or prevention of liver disease. For example, an important issue

is response to vaccinations against the hepatitis A virus (HAV) and HBV, which is often suboptimal in HIV-infected individuals.

- *Research Goal:* To develop improved approaches to HAV and HBV vaccination in HIV-infected persons, including better regimens of administration and more potent vaccines (Matrix Cell A1).

Cohorts of HIV-infected patients could also be evaluated for environmental and genetic risk factors contributing to the development of fatty liver disease and drug-induced liver injury. The incidence of these problems is unknown in this population.

Importantly, better means of diagnosis, including grading and staging of liver disease, would greatly benefit HIV-positive persons. Indeed, the clinical and serum biochemical markers for the presence and severity of liver disease that are used in HIV-negative populations may be less reliable in HIV-infected persons. Thus, serum aminotransferase levels, which are routinely used to monitor disease activity of hepatitis and nonalcoholic fatty liver disease, appear to be inappropriately low in patients with HIV infection and these liver diseases. Furthermore, the presence of multiple causes of liver disease makes specific diagnosis of fatty liver disease or drug-induced liver disease difficult.

- *Research Goal:* To identify better means to reliably attribute causality to drug-induced liver disease and to detect and assess fatty liver injury in HIV-infected patients (Matrix Cells C2 and C3; see also Chapter 8, A1).

Metabolomic approaches may be useful in achieving these goals.

At present, liver biopsy is the gold standard for assessing disease activity (grade) and fibrosis (stage of disease). Until better diagnostic aids and noninvasive tests are available, it is appropriate that liver biopsy be increasingly applied to HIV-positive populations to provide accurate information on the prevalence, etiology, and severity of liver disease. However, liver biopsy has many shortcomings, including discomfort, risk, cost, and problems with sampling error and observer variation in scoring. Application of proteomics and gene array approaches to serum and liver tissue in prospectively followed, well characterized patients with HIV infection and liver disease will undoubtedly lead to more insights into the causes of disease progression and worsening of fibrosis and will likely provide a basis for the development of noninvasive biomarkers to grade and stage disease.

- *Research Goal:* To identify biomarkers that accurately reflect disease activity and stage (Matrix Cell C2; see also: Chapter 2, A3; Chapter 7, B2; Chapter 16, C1).

These studies could be compared and contrasted to similar studies in patients with liver disease without HIV. Such comparisons are likely to provide new insights into the interactions between HIV, hepatitis viruses, and liver disease. Such studies could also be combined with genetic analyses focusing on genes that modify the course and outcome of liver disease. Patients with HIV infection appear to have more rapid progression of chronic hepatitis B and C with more rapid worsening of hepatic fibrosis.

- *Research Goal:* To identify factors that mediate the accelerated course of hepatitis B and C in HIV-infected individuals, with a focus on genetic and environmental, as well as viral factors and the role of antiretroviral medications (Matrix Cell B2).

Clinical Investigation of Therapy: Although hepatitis B and C appear to be more rapidly progressive in persons with HIV infection than in those without, therapies for these diseases are usually applied to HIV-positive cohorts only after their extensive evaluation in

non-infected patients. This delay in application of new therapies for liver disease to HIV-positive persons should be remedied and new treatments tested earlier in this group. Indeed, because hepatitis B and C tend to be more rapidly progressive in HIV-positive patients, studies of new therapies in this group are more likely to produce information on important outcomes in a shorter timeframe.

The types of clinical trials that could be performed in HIV cohorts to adequately address these and other current issues related to liver disease are many, and only a few examples can be listed here, including studies of:

- Response rates and tolerance of peginterferon and different doses of ribavirin in selected cohorts of patients with HIV-HCV coinfection (e.g., patients with early disease not on ART therapy, patients with worsening HIV infection and low CD4+ T cell counts, patients with hemophilia, patients with continuing substance abuse, patients with poor social support systems, HIV-positive patients with cirrhosis, and children) (Matrix Cell A1);
- Efficacy and safety of long-term maintenance peginterferon with or without ribavirin in patients with chronic hepatitis C who fail to respond to optimal current therapy (Matrix Cell B1);
- Safety and efficacy of new agents introduced for therapy of hepatitis C (Matrix Cell C1);
- Pharmacokinetic profiles of different combinations of anti-hepatitis and anti-HIV medications to determine potential drug interactions;
- Role of the GB virus C (GBV-C), which is closely related to HCV, in the natural history of HIV infection as affected by antiviral therapy for hepatitis C, which may result in clearance of GBV-C;
- Rates of adherence, safety and response to peginterferon and ribavirin in HIV-infected persons with active substance abuse;
- Effect of alcohol and alcohol treatment programs or therapy for HCV or HBV on immune responses to HIV (and hepatitis viruses) in coinfected persons;
- Role of early therapy for acute HCV infection in HIV-infected persons (Matrix Cell A2);
- Optimal regimen of anti-HBV medications in patients on ART, including use of HBV-specific therapies (e.g., entecavir, telbivudine, or beta-L-thymidine, L-dT) in patients with HIV coinfection (as opposed to tenofovir disoproxil fumerate or lamivudine, which are active against both viruses) (Matrix Cell C1);
- Other means of improving outcome of hepatitis B or C, such as use of growth factors and antidepressants to alleviate side effects of combination therapy, innovative approaches to improve adherence, use of support groups, and concurrent therapy with nonspecific agents such as antioxidants and herbal medications; and
- Use of specific therapies (e.g., insulin-sensitizing agents, anti-oxidants) for nonalcoholic steatohepatitis in HIV-infected persons.

A special problem for combination therapy of HBV or HCV in HIV-infected persons receiving ART is lactic acidosis due to hepatic mitochondrial injury. Several nucleoside analogues with activity against HBV and HIV (e.g., fialuridine, didanosine, stavudine) have been shown to cause severe mitochondrial DNA damage with manifestations such as lactic acidosis and liver failure, pancreatitis, myopathy, and neuropathy, especially in conjunction with ribavirin treatment. Better understanding of this syndrome, including its pathogenesis, risk factors, natural history and therapy, would be helpful. In most patients, this syndrome is reversible if it is recognized early and medications withdrawn rapidly. However, the diagnosis is difficult.

- *Research Goal:* To develop more reliable, noninvasive means of assessing mitochondrial function and injury (Matrix Cell B3).

These diagnostic tests could include imaging techniques to detect microvesicular steatosis or changes

in ATP levels in tissue and biomarkers in serum or urine that reflect mitochondrial function or damage. Such assays would help to demonstrate frequency of subclinical degrees of mitochondrial injury in liver and muscle and allow for better detection and elucidation of the pathogenesis of this potentially fatal syndrome.

These goals to improve therapeutic management of liver disease in HIV-infected persons through NIH-driven research would be complemented by the efforts of other entities that specialize in determining and encouraging use of current best practices by health care providers and their patients through educational and outreach programs.

STEPS TO ACHIEVE RESEARCH GOALS

Collaborations between basic researchers, virologists, immunologists, and cell biologists interested in HIV, viral hepatitis, and liver disease would be beneficial to advancing this research. A high priority could be placed on identifying approaches to develop animal models of coinfection or *in vitro* cell culture systems to study both direct and indirect HIV-HCV and HIV-HBV interactions.

Large cohort studies on the clinical course and natural history of HIV infection could be augmented with studies of liver disease. Again, collaborations between medical providers with expertise in HIV infection and those with knowledge of liver disease could ensure that optimal approaches are taken to the investigation of liver disease and its therapy in HIV-infected persons. In this regard, the recent strengthening of hepatologic expertise in the AIDS Clinical Trials Group (ACTG) is likely to be very helpful. In particular, expertise in drug-induced liver disease would be useful in assessing cohorts of patients on ART therapy with prospective application of rigorous approaches to evaluating causality in these patients who often have multiple possible reasons for their liver disease.

Most importantly, advances could be gained from the application of prospective randomized controlled trials of liver disease therapy to large groups of HIV-infected patients. Furthermore, an effort could be made to optimize the amount of information that can be obtained from such trials using ancillary studies of biomarkers for fibrosis, gene array studies of factors associated with high rate of progression or poor response to treatment, and metabolomic and proteomic studies of liver disease.

Matrix of Research Goals in HIV and Liver Disease

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** Define effects of HIV infection on the liver, including on different populations of liver cells.	**B3.** Develop noninvasive means of detecting early hepatic mitochondrial dysfunction.	**C3.** Develop *in vitro* or *in vivo* models of HIV-HCV and HIV-HBV coinfection. Develop means to reliably attribute causality of drug-induced liver disease in HIV-infected persons.
Intermediate Risk	**A2.** Define safety and efficacy of peginterferon therapy for acute hepatitis C in HIV coinfection.	**B2.** Elucidate mechanisms by which HIV infection accelerates fibrosis and disease progression in HBV and HCV infection. Define factors that lead to reactivation of HBV in HIV coinfection and develop means of prevention.	**C2.** Develop noninvasive means of assessing liver disease stage and activity in HIV-infected persons.
Low Risk	**A1.** Develop improved regimens of HAV and HBV vaccination. Define short- and long-term safety and efficacy of peginterferon and ribavirin in different subpopulations of patients with HIV-HCV coinfection.	**B1.** Define whether long-term peginterferon slows progression of disease in chronic hepatitis C with HIV coinfection. Define prevalence, etiology, and severity of different liver diseases in different cohorts of HIV-infected patients.	**C1.** Develop optimal therapeutic regimens for chronic hepatitis B in different stages and patterns of disease in HIV-coinfected patients. Define safety and efficacy of new agents for therapy of hepatitis C in HIV coinfection.